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SCIENCE MEDICINES HEALTH

Advancing acceptance of 3Rs testing approaches for regulatory testing of medicinal products in the EU
The EMA 3Rs Working Party

EMA Veterinary Awareness Day

Presented by Sonja Beken on 13 September 2023
3Rs Working Party (EMA)

Outline

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- Drivers for 3Rs
- EMA’s commitment to 3Rs – historical perspective
- Introducing the new 3RsWP
- … and its ambitious 3Rs Workplan
- Take home messages

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Animal experimentation in Europe – regulatory use

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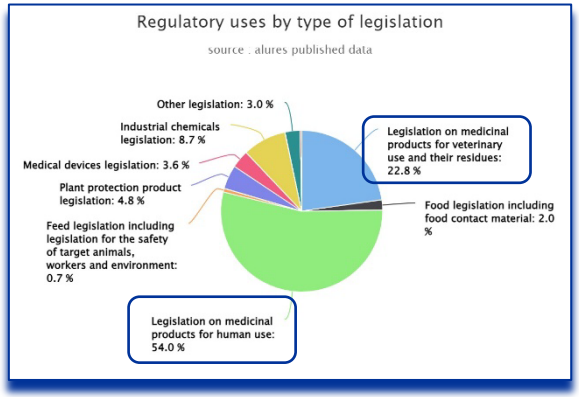
7,9 million animals in 28 Member States (EU-27 & Norway - 2020)

Publicly accessible ALURES Statistical EU Database on animal use



Human Medicinal Products

Regulatory uses: Toxicity	Number of uses	Percentage
Pharmaco-dynamics (incl safety pharmacology)	54886	28.62%
Kinetics	42320	22.07%
Repeated dose toxicity	48406	25.24%
Acute and sub-acute	8494	4.43%
Skin irritation/corrosion	517	0.27%
Ecotoxicity	5869	3.06%
Skin sensitisation	4015	2.09%
Other toxicity/safety testing	1247	0.65%
Developmental toxicity	15319	7.99%
Eye irritation/corrosion	141	0.07%
Safety testing in food and feed area	1	0.00%
Genotoxicity	1850	0.96%
Reproductive toxicity	6460	3.37%
Phototoxicity	74	0.04%
Carcinogenicity	1008	0.53%
Neurotoxicity	22	0.01%
Target animal safety	1146	0.60%
Total	**191775**	**100,00%**

Regulatory uses: Quality control	Number of uses	Percentage
Batch safety testing	68571	13.21%
Batch potency testing	414764	79.88%
Other quality controls	14376	2.77%
Pyrogenicity testing	21545	4.15%
Total	**519256**	**100,00%**

Veterinary Medicinal Products

Regulatory uses: Toxicity	Number of uses	Percentage
Acute and sub-acute	17169	34.62%
Kinetics	938	1.89%
Target animal safety	24115	48.63%
Pharmaco-dynamics (incl safety pharmacology)	985	1.99%
Other toxicity/safety testing	4413	8.90%
Safety testing in food and feed area	767	1.55%
Repeated dose toxicity	204	0.41%
Skin sensitisation	574	1.16%
Ecotoxicity	246	0.50%
Skin irritation/corrosion	9	0.02%
Developmental toxicity	145	0.29%
Genotoxicity	27	0.05%
Total	**49592**	**100,00%**

Regulatory uses: Quality control	Number of uses	Percentage
Batch safety testing	68910	29.04%
Batch potency testing	162770	68.59%
Other quality controls	5187	2.19%
Pyrogenicity testing	435	0.18%
Total	**237302**	**100,00%**

Directive 2010/63/EU of the EP and of the Council

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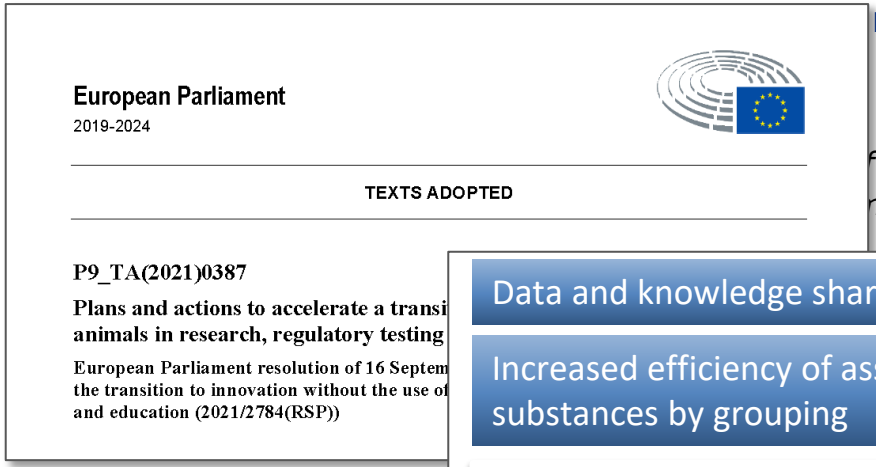


European Parliament
2019-2024

TEXTS ADOPTED

P9_TA(2021)0387

Plans and actions to accelerate a transi
animals in research, regulatory testing

European Parliament resolution of 16 Septem
the transition to innovation without the use of
and education (2021/2784(RSP))

mals used for scientific purposes

scientifically satisfactory method or testing strategy, not
f a procedure.
nals used in projects is reduced to a minimum without

procedure is not carried o
the use of a live animal, is
2. In choosing between pro
selected:
(a) use the minimum nu
(b) involve animals with
(c) cause the least pain,
and are most likely to pr

Data and knowledge sharing: PARERE and other mechanisms

10/02/2022

Increased efficiency of assessing substances by grouping

One substance – One assessment, see 'ONE – Health, Environment, Society - Conference', June 2022 Brussels

3Rs in R&D of medicines EMA and 3Rs

ALURES statistical database and open-access database on non-technical summaries of authorised projects

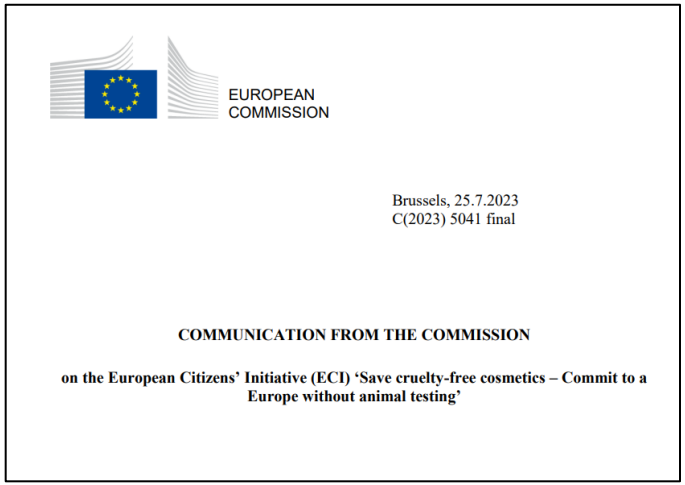
IMI and H2020/Horizon Europe and European Research Council

EURL-ECVAM reviews on NAMs in biomedical research

Training programmes on 3Rs

EPAA as means for collaboration

European Citizen's Initiative:
Save cruelty-free cosmetics – Commit to a Europe without animal testing



EC roadmap to **reduce animal testing** as pre-requisite to **transition towards animal free regulatory system**

Multistakeholder workshops to discuss roadmap and present & discuss progress

Close collaboration with agencies (e.g. EMA), Member States and relevant stakeholders

Analysis of the need and feasibility of expert scientific committee to provide advice on development and regulatory uptake of 3Rs methods or Novel Approach Methods (NAMs)

Introductory considerations

European Commission

- Reference to Directive 2010/63/EU and its 3Rs principles
- Avoidance of unnecessary duplication of animal testing:
  - *procedures to facilitate joint animal testing where possible*
  - *reuse of animal study results and public availability of animal study result*
- One-Substance-One-Assessment for environmental risk assessment (ERA)

Articles

- Demonstration of 3Rs compliance by marketing authorization (MA) applicants and holders

  "The MA applicant shall demonstrate that the principle of 3Rs of animal testing for scientific purposes has been applied in compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application"

  "The MA applicant shall not carry out animal tests in case scientifically satisfactory non-animal testing methods are available"
- Definition of a non-clinical test = *in vitro, in silico, in chemico* and non-human *in vivo* testing:
- Product specific validation to replace animal-based batch release testing as condition for marketing authorisation
- EMA responsibilities with regards to animal use and the 3Rs
- Joint ERA studies to avoid unnecessary duplication of animal studies

Reducing drug attrition through better prediction

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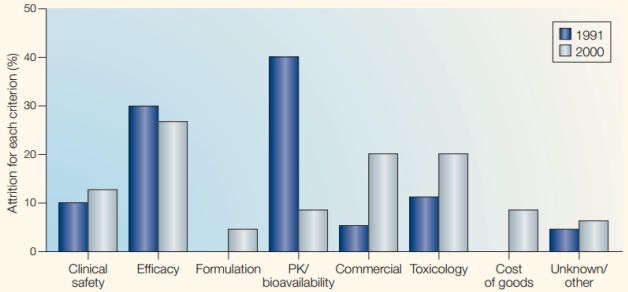
Kola and Landis 2004

Nature Reviews Drug Discovery 3, 711-715



Hornberg et al 2014

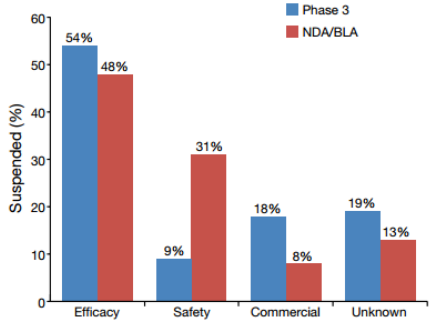
Drug Discovery Today 19; 1131-1136

Most noted safety reasons for withdrawal of marketed drugs:

- *Liver toxicity*
- *Cardiovascular toxicity*
- *CNS effects*

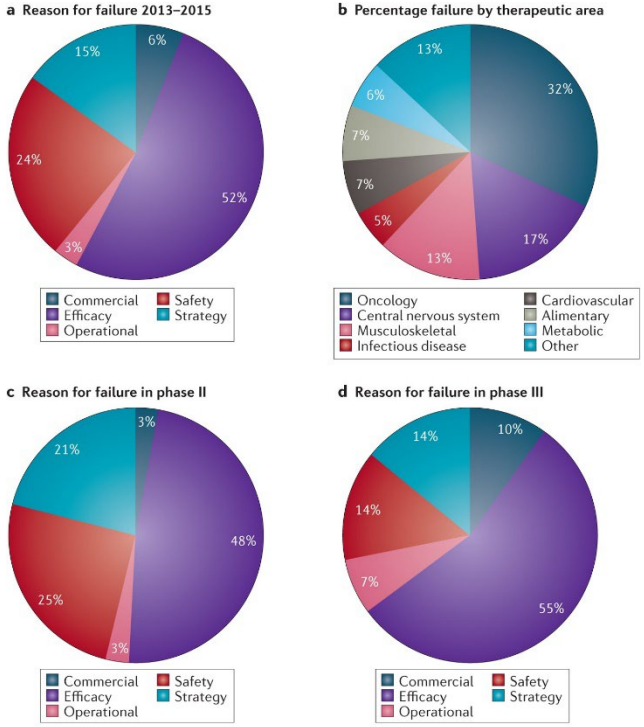
Hay et al, 2014,

Nature Biotechnology 21; 40-51



Harrison, 2016,

Nature Reviews Drug Discovery 15; 817-818



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EMA's commitments to the 3Rs

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Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Human regulatory

Overview | Research and development | Marketing authorisation

Post-authorisation | Herbal products

- Adaptive pathways
- Advanced therapies
- Clinical trials
- Compassionate use
- Compliance
- Data on medicines (ISO IDMP standards)
- Ethical use of animals
- Innovation in medicines
- Medicines for older people
- Orphan designation
- Paediatric medicines
- Pharmacovigilance
- PRIME: priority medicines

Ethical use of animals in medicine testing

Share

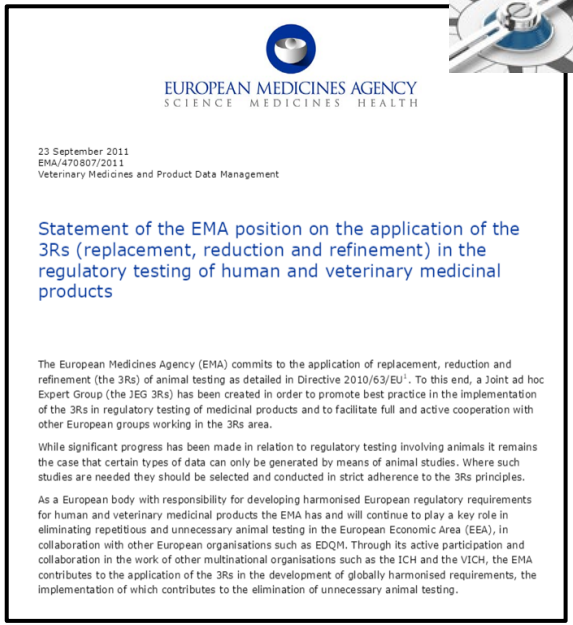
Table of contents

This content applies to human and veterinary medicines

The European Medicines Agency (EMA) supports the implementation of the so-called 3Rs principles - replace, reduce and refine - for the ethical use of animals in medicine testing across the European Union (EU). These principles encourage alternatives to the use of animals in the testing of medicines while safeguarding scientific quality and improving animal welfare where the use of animals cannot be avoided.

Directive 2010/63/EU requires marketing authorisation holders to integrate the 3Rs and welfare standards for the treatment of animals in all aspects of the development, manufacture and testing of medicines.

The Directive aims to **protect animals** in scientific research, with the final aim of replacing all animal research with non-animal methods.



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23 September 2011
EMA/470807/2011
Veterinary Medicines and Product Data Management

Statement of the EMA position on the application of the 3Rs (replacement, reduction and refinement) in the regulatory testing of human and veterinary medicinal products

The European Medicines Agency (EMA) commits to the application of replacement, reduction and refinement (the 3Rs) of animal testing as detailed in Directive 2010/63/EU[1]. To this end, a Joint ad hoc Expert Group (the JEG 3Rs) has been created in order to promote best practice in the implementation of the 3Rs in regulatory testing of medicinal products and to facilitate full and active cooperation with other European groups working in the 3Rs area.

While significant progress has been made in relation to regulatory testing involving animals it remains the case that certain types of data can only be generated by means of animal studies. Where such studies are needed they should be selected and conducted in strict adherence to the 3Rs principles.

As a European body with responsibility for developing harmonised European regulatory requirements for human and veterinary medicinal products the EMA has and will continue to play a key role in eliminating repetitious and unnecessary animal testing in the European Economic Area (EEA), in collaboration with other European organisations such as EDQM. Through its active participation and collaboration in the work of other multinational organisations such as the ICH and the VICH, the EMA contributes to the application of the 3Rs in the development of globally harmonised requirements, the implementation of which contributes to the elimination of unnecessary animal testing.

Achievements of the JEG3Rs & J3RsWG (2010-2017)

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Setting up a regulatory framework to foster uptake of 3R testing approaches

- Guideline on basic principles of regulatory acceptance of NAMs/3Rs for testing of HMPs and VMPs
- Review and update of EMA and (V)ICH guidelines to implement 3Rs best practices
- Guidance for individual laboratories for transfer of 3R quality control methods validated in collaborative trials
- Position statement on the ethical use of animals in the development, manufacture and testing of VMPs

3Rs in Batch Release testing

- Review of final product batch testing requirements
- Recommendation to MAHs to foster use of 3Rs methods in line with the European Pharmacopoeia
- Training for assessors

Collaboration with EU & international organisations

(e.g. EC, EDQM, EURL-ECVAM, other EU agencies)

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EMA's Regulatory Science Strategy (RSS 2025)

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Core recommendations dedicated to the 3Rs

- Raising awareness for 3Rs/NAMs and regulatory acceptance
- Need for discussion on criteria for regulatory acceptance → qualification, context of use, endpoints and reference compounds
- Engagement with stakeholders → European regulatory network on NAMs
- Focal role of a 3Rs Working Party

The new 3Rs working party (3RsWP)

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Strategic and visible Working Party to monitor and supervise EMA's 3Rs activities

Multidisciplinary aspects of the 3Rs into a restricted core working group

Sonja Beken (Chair)	BE	FAGG-AFMPS-FAMHP	Human MPs - NCWP, Non-Clinical
Sarah Adler-Flindt (Vice-Chair)	DE	Federal Office of Consumer Protection and Food Safety	Veterinary MPs - Non-Clinical
Elisabeth Balks	DE	PEI	Veterinary MPs - Batch release
Kathrine Just Andersen	DK	Danish Medicines Agency	Veterinary MPs - EWP-V, Non-Clinical and Clinical
Camilla Svensson	SE	MPA	Human MPs - Non-Clinical
Peter Theunissen	NL	MEB	Human MPs - Non-Clinical

Support by:

- Operational Expert Groups (OEG Batch release testing) & Drafting Groups
- Non-Clinical and New Approach Methodologies European Specialised Expert Community →
- EMA: 3Rs@ema.europa.eu
  - Scientific secretariat: Stefano Ponzano and Orla Moriarty (H-Division), Michael Empl (Vet-division)
  - Administrative secretariat: Stavroula Tasiopoulou (H-division)
- Observers: European Commission, EURL ECVAM, EDQM

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EUROPEAN MEDICINES AGENCY

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An ambitious 3Rs workplan with a vision to the future

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High level strategic goals:

- Strategic role in the field of the 3Rs with strengthened cooperation between all stakeholders and international partners
- Move non-clinical assessment from discovery toxicology towards regulatory use and acceptance of animal-free innovations or NAMs
- Follow-up of the 3Rs in batch release testing of human and veterinary medicinal products
- Review and update of EMA guidelines to implement 3Rs best practices and monitor the impact of implemented changes
- Follow up of actions following EP resolution on plans and actions to accelerate the transition to innovation without the use of animals (2021/2784(RSP)
- Follow-up and identify actions related to alternatives to the use of non-human primates

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26 January 2023
EMA/CHMP/14829/2023
Human Medicines Division

Consolidated 3-year work plan for the Non-clinical domain including the priorities for 2023

Domain Chairperson:	Bruno Sepodes
Non-Clinical Working Party Chair:	Susanne Brendler-Schwaab
Non-Clinical Working Party Vice-Chair:	Karen van Malderen
3Rs Working Party Chair:	Sonja Beken
3Rs Working Party Vice-Chair:	Sarah Adler-Flindt

Work plan period: May 2022 – December 2024 (with a first review point after one year)

3RsWP Workplan – Guideline activities for 2023

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- **New** Reflection Paper on alternatives to the use of non-human primates (*in collaboration with Non-Clinical Working Party*)

- **Revision** of the Guideline on principles of regulatory acceptance of 3Rs testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)
  - Inclusion of definition of critical 3Rs-related terminology
  - Inclusion of annexes providing regulatory acceptance criteria for microphysiological systems (MPS), including Organ-on-Chip (OoC) models for specific contexts of use to be applied in the pharmaceutical area

- **Revision** of Reflection Papers providing an overview of current regulatory testing requirements and opportunities for 3Rs implementation
  - for human medicinal products (EMA/CHMP/CVMP/3Rs/742466/2015)
  - for veterinary medicinal products (EMA/CHMP/CVMP/3Rs/164002/2016)

3RsWP Workplan – Regulatory Acceptance of NAMs/3Rs

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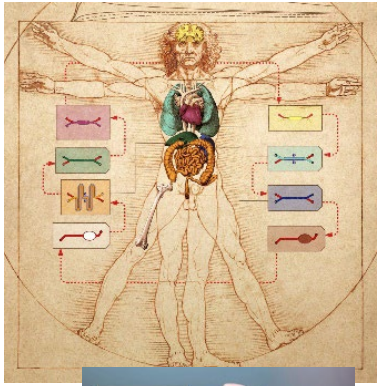
Development of COU-based qualification criteria

Qualification of NAMs

- Multistakeholder workshops on MPS/OoC models
- Definition of regulatory acceptance criteria for MPS/OoC for specific contexts of use
- Creation of a worldwide cluster of regulators (harmonization!)
- Collaboration with EMA Methodology domain on modelling and simulation
- Support qualification of NAMs & follow up of 3Rs impact:
  - for embryofetal development testing (ICHS5R3)
  - for cardiovascular safety pharmacology testing (Q&A ICHS7B)
  - For skin sensitization testing (OECD)
- Support the Innovation Task Force and the Scientific Advice Procedure



Collaboration with EMA's Innovation Task Force on 3Rs

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- Dedicated forum for early dialogue between regulators and stakeholders → SMEs, academics, researchers, research and public-private funded consortia, pharmaceutical industry)
- NEW focus on regulatory acceptance of NAMs to replace the use of animals in the testing of medicines (3Rs)
  e.g., in silico modelling & novel in vitro assays (e.g. MPS/OoC)
- Objectives: encourage the development of NAMs & accelerate their integration in the regulatory framework for the development and evaluation of medicines
- Informal exchange of information and provision of guidance (non-legally binding) early in the development process during briefing meetings
- Discussion led by multidisciplinary experts from the Agency network, and EMA working parties & committees – best available scientific expertise
- The briefing meetings are free of charge

3RsWP Workplan – Other activities

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2023

- Review of product batch release testing requirements
- Annual multistakeholder 3RsWP meetings
- Mapping of cooperation with EU and International NAM/3Rs stakeholders
- Training on 3Rs methods & best practices
- Follow up on 3Rs in new draft Commission proposal for the Pharmaceutical Legislation

Beyond 2023

- EMA 3RsWP multistakeholder conference: showcase 3Rs progress, introduce 3RsWP & future workstreams (3Rs Roadmap)
- Review of most promising available 3Rs methods to consider for qualification
- Establish an easily accessible database for qualified/validated NAMs (with EDQM & EURL-ECVAM)

First 3RsWP Annual Stakeholder Meeting – 28/02/2023

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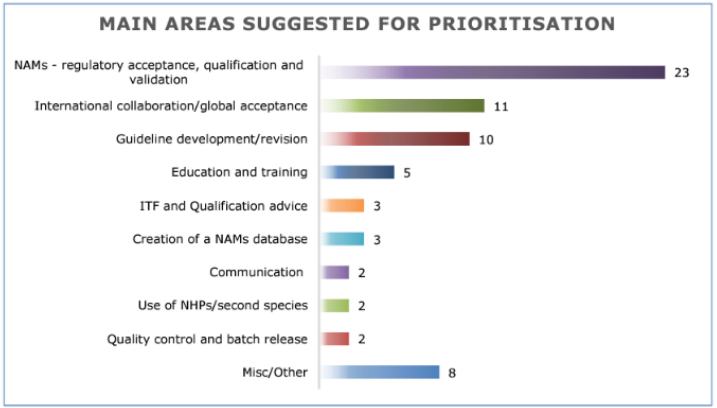
- Stakeholders (upon invitation):
  - Industry & CROs
  - EU agencies & organisations
  - NGOs & animal welfare associations
  - Research consortia & other stakeholders

- Agenda :
  - Introductory public session → live broadcast with interactive SLIDO
  - Closed sessions per stakeholder group
  - Topics proposed by the invited stakeholders

- Outcome:
  - Constructive discussions with all stakeholders
  - Emphasis on current workplan actions
  - Additional topics to be considered for future actions
  - Public Session Report



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Take home messages

Historically the EU Regulatory Network has been open to 3Rs

EMA is clearly committed to the 3Rs

3RsWP is EMA's official 3Rs hub

3Rs strategy & ambitious workplan in place to support the work

Engagement & open dialogue with interested 3Rs stakeholders

Close collaboration with ITF 3Rs as essential tool for early engagement

Global regulatory collaboration is key

Thank you for your attention! Any questions? Suggestions?

Further information

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